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Title: Baseline predictors of vitreomacular adhesion/traction resolution following an intravitreal injection of ocriplasmin

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Abstract

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Background and Objective: To determine factors predicting ocriplasmin response in patients with symptomatic vitreomacular adhesion (VMA).

Patients and Methods: Combined analysis of 2 multicenter, prospective, randomized, double-blind, trials of intravitreal ocriplasmin 125µg injection vs placebo. Patients had vitreomacular traction with or without a full-thickness macular hole (FTMH). Multivariate logistic regression was used to determine factors influencing treatment response (complete VMA release [day 28] and nonsurgical FTMH closure [month 6]).

Results: Younger age, presence of FTMH (odds ratio [OR]=2.1; 95% confidence interval [CI]: 1.1, 3.7), VMA diameter ≤1500µm (OR=4.9; 95%CI: 2.0, 12.4), phakic lens status (OR=2.8; 95%CI: 1.5, 5.2), and absence of epiretinal membrane (OR=4.1; 95%CI: 2.2, 7.9), predicted VMA resolution. FTMHs with apical diameter ≤250µm were more likely to close than larger holes (58.3% vs 24.6%; *P*=0.013). Both size groups had significantly greater chance of VMA resolution and FTMH closure vs controls.

Conclusion: Ocriplasmin is most effective in younger patients with focal VMA and without an epiretinal membrane.

Introduction

Vitreomacular traction (VMT) occurs in the context of perifoveal vitreous detachment, where residual foveal adhesion leads to distortion of the foveal architecture.[1] Minor degrees of anatomic disturbance are compatible with normal vision, but if the traction progresses it can lead to troublesome metamorphopsia and blurred vision.[2] Traction can also progress to a full-thickness macular hole (FTMH).[1-4]

The current standard of care for VMT is either observation or pars plana vitrectomy. Observation is usually appropriate for patients who are either asymptomatic or mildly symptomatic, and some cases may resolve spontaneously over time.[5,6] In the pre-optical coherence tomography (OCT) era, a natural history study found that only 11% of cases resolved over 5 years, with almost two-thirds of eyes losing at least two Snellen lines over this time frame.[7] In a more recent retrospective chart review of 106 eyes (81 patients) followed with spectral-domain OCT for a mean duration of 23 months, VMA was found to resolve spontaneously in 32% of eyes.[8]

Pars plana vitrectomy is highly effective at relieving VMT, but the visual acuity (VA) gains may be modest, and vitrectomy is not without risk. A meta-analysis of vitrectomy for VMT reported that only one-third of eyes gained at least two Snellen lines.[9] Postoperative retinal detachment occurred in 4.6% of eyes, and 63% of phakic eyes developed cataract.[9]

More recently, Stalmans et al reported a Phase 3, double-masked, placebo-controlled study of ocriplasmin for the treatment of VMT.[10] Ocriplasmin (Jetrea®, ThromboGenics NV, Leuven, Belgium)[11,12] is a truncated form of plasmin, designed to liquefy the vitreous and resolve vitreomacular adhesion (VMA).[13-15] Following a single intravitreal injection of ocriplasmin 125 µg, 26.5% of eyes had complete resolution of VMA at the 28 day primary endpoint, vs 10.1% of the control (placebo) eyes.[10] In eyes with coexisting FTMHs, 40.6% had hole closure by day 28, compared with 10.6% in the placebo group. There was a favorable safety profile, with many of the adverse events attributable to successful posterior vitreous detachment (PVD).[10]

The combined pivotal trial of ocriplasmin met its primary endpoint, with significantly greater VMA resolution in the ocriplasmin group.[10] A predefined, wide-ranging subgroup analysis of one or more of the 15 baseline variables was undertaken in relation to the primary and some of the secondary outcomes. This suggested that there were five factors that may help predict a positive anatomic response to ocriplasmin, namely age younger than 65 years, eyes without an epiretinal membrane (ERM), eyes with a FTMH, phakic eyes, and eyes with a focal VMA ≤1500 µm.[16] Macular holes with an apical diameter of ≤250 µm were more likely to achieve nonsurgical closure than larger FTMHs. Visual acuity was more likely to improve in patients younger than 65 years and in eyes with a lower

best-corrected visual acuity at baseline. The initial subgroup analyses[16] were not designed to provide detailed or targeted outcome data in those eyes identified as being potentially more responsive to ocriplasmin. We therefore aimed to undertake a post hoc best-responder analysis to refine our understanding of the outcomes in eyes thought most likely to respond to ocriplasmin, and thereby generate assumptions and hypotheses that can be tested in further definitive trials.

Patients and Methods

Details of the patient population, study design, and efficacy assessments for the two multicenter, randomized, double-masked, placebo-controlled, Phase 3 studies (TG-MV-006, NCT00781859 and TG-MV-007, NCT00798317) have been published.[10] Data from both trials were pooled for a prespecified combined analysis. The trials recruited adult participants with OCT-confirmed VMA, and those with FTMH of up to 400 µm, provided the FTMH occurred in association with VMA. Best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) VA had to be at least 20/25 in the study eye. Epiretinal membranes were not excluded. In total, 652 patients (652 eyes) were randomized to receive a single intravitreal injection of ocriplasmin 125 µg in a 0.10-mL volume, or a placebo injection containing the same vehicle and fluid volume. Institutional review board or ethics committee approval was obtained for each participating site, and all participants provided written informed consent. The studies adhered to the tenets of the Declaration of Helsinki.

Participants underwent a full ophthalmic examination and an OCT at baseline, then at 7, 14, 28, 90, and 180 days after injection. A central OCT reading center determined if VMA or macular hole was present or absent, at each visit.

To evaluate which baseline characteristics would predict the primary efficacy endpoint (VMA resolution at day 28) and non-surgical FTMH closure at month 6, multivariate logistic regression models were built. Although a subgroup analysis was preplanned, it was post hoc with respect to the original analyses of the individual trials (TG-MV-006 and TG-MV-007), which did not incorporate a subgroup analysis. The demographic covariates analyzed for their effects on the two efficacy endpoints included one or more of the following: age (<65 years, 65 to 75 years, and >75 years); gender; geographic region (US vs EU); race (white vs non-white); and body mass index (BMI <25 kg/m^2 vs ≥25 kg/m^2). Covariates for baseline disease characteristics included one or more of the following: presence/absence of ERM; diameter of focal VMA (>1500 µm vs ≤1500 µm); presence/absence of FTMH; lens status (phakic vs pseudophakic); presence/absence of diabetic retinopathy; expected need for vitrectomy at baseline (yes vs no); and VA (<65 letters, 65 to 75 letters, and >75 letters). Additional baseline variables were assessed for the FTMH closure endpoint including maximum FTMH base diameter, measured at the retinal pigment

epithelium (>600 µm vs ≤600 µm), and the apical diameter (>250 µm vs ≤250 µm). Macular hole width was determined by taking the minimal intraretinal width measurements, roughly parallel to the retinal pigment epithelium (RPE), for each line scan where a full-thickness defect was present. The largest width recorded was used as the macular hole width measurement for the studies. Figure 1 shows OCT images illustrating how eyes were classified.

Covariate evaluations were first performed in a univariate manner by adding the covariates individually to the model. A 0.05 level was considered significant. If the covariate was not significant at the 0.05 level (type 3 test), it was not included in the final multivariate model. The variables of treatment and study (TG-MV-006 vs TG-MV-007) were always included in the univariate and multivariate models. Covariates found significant in the multivariate model were then defined as predictive; their corresponding odds ratios (ORs) are presented. The ORs were computed with their 95% confidence interval (CI). Statistical analyses were performed using SAS® version 9.1.3.

Results

Demographic and baseline characteristics

Of the 652 participants in studies TG-MV-006 and TG-MV-007, 464 were randomized to receive an intravitreal ocriplasmin injection and 188 received an intravitreal placebo injection.[10] The study groups had similar demographics and baseline disease characteristics, except that the ocriplasmin group had a higher percentage of pseudophakic eyes (37.1% vs 28.2% for ocriplasmin and placebo, respectively). Baseline demographic and disease characteristics have been previously published.[16]

Baseline predictors of VMA resolution

Resolution of VMA at day 28 (the primary endpoint) was achieved in significantly more patients treated with ocriplasmin than with placebo (26.5% vs 10.1%; *P*<0.001).[10] The significance of this treatment effect was confirmed by a multivariate logistic regression analysis. In the multivariate model adjusted for baseline covariates, treatment with ocriplasmin had a significant effect on the proportion of patients achieving VMA resolution at day 28 (*P*<0.001; OR=6.0; 95% CI: 3.2, 11.4).

Multivariate logistic regression model found that age was predictive of VMA resolution (type 3 test, *P*<0.001). Younger patients were more likely to have a VMA release than older patients. Resolution of VMA occurred in 38/80 (47.5%) ocriplasmin-treated patients aged <65 years vs 85/384 (22.1%) of those aged ≥65 years. In both age groups, VMA resolution was significantly more common in the ocriplasmin group than in the placebo group with 10/43 (23.3%) placebo-treated patients aged <65 years responding vs 9/145 (6.2%) of those aged ≥65 years.

The multivariate logistic regression model also found that anatomic features significantly predictive of VMA resolution included the presence of FTMH (OR=2.053; 95% CI: 1.126, 3.742; *P*=0.019), VMA diameter ≤1500 µm (OR=4.944; 95% CI: 1.965, 12.435; *P*<0.001), phakic lens status (OR=2.824; 95% CI: 1.536, 5.192; *P*<0.001), and absence of an ERM (OR=4.149; 95% CI: 2.183, 7.937; *P*<0.001) (Figure 2). The percentages of participants that achieved VMA resolution at day 28 in each of the independently predictive covariate subgroups are shown in Figure 3. Across these subgroups, VMA resolution was achieved in 50.0% of ocriplasmin recipients and 25.5% of placebo recipients. Treatment differences in favor of ocriplasmin were observed across all subgroups compared with controls.

Baseline predictors of FTMH closure

Across the two studies, the proportion of participants who achieved nonsurgical FTMH closure at day 28 was significantly higher in the ocriplasmin group (40.6%) than in the vehicle group (10.6%) (OR=5.94; 95% CI: 2.09, 21.01; *P*<0.001).[10] Similar results were observed at month 6 (40.6% vs 17.0%; OR=3.45; 95% CI: 1.40, 9.49; *P*=0.004). Multivariate analysis demonstrated that treatment with ocriplasmin was an independent predictor of FTMH closure by month 6 (OR=4.267; 95% CI: 1.714, 10.623; *P*=0.002 [Figure 4]). Recruitment to either of the pivotal trials (TG-MV-006 or TG-MV-007) did not affect outcome.

Using the multivariate model, eyes with an FTMH apical diameter ≤250 µm were more likely to achieve nonsurgical closure by month 6 than eyes with a hole >250 µm (58.3% vs 24.6%, respectively; OR=2.724; 95% CI: 1.237, 6.001; *P*=0.013 [Figures 4 and 5]). The forest plot (Figure 4) shows that eyes with a macular hole base diameter (Max MH width at RPE) ≤600 µm tended to do better than larger holes, but this did not reach significance. However, both size groups had a greater chance of FTMH closure than controls, with a treatment difference of 38.3% (95% CI: 17.3, 59.3) for FTMHs ≤250 µm and 10.9% (95% CI: −7.3, 29.1) for those >250 µm. The percentages of patients that achieved macular hole closure at month 6 in each of the FTMH baseline width subgroups are shown in Figure 5.

Discussion

Ocriplasmin is a first-in-class drug that leads to a significantly higher rate of VMA resolution compared with placebo injection. However, it would be helpful for the clinician to know which patients respond best to treatment with ocriplasmin. Targeted case selection is likely to increase the rate of VMA resolution that occurs following ocriplasmin injection. For patients with VMT, our analysis suggests that ocriplasmin is most effective for eyes with focal VMA (≤1500 µm) and without an ERM. For eyes with FTMH, closure is more likely if the apical hole diameter is ≤250 µm.

The better response in eyes with focal VMA and no ERM is biologically plausible. Ocriplasmin liquefies the vitreous and resolves adhesions at the vitreomacular interface,[13,15] but it does not exert the kind of tractional force that can be achieved during macular surgery. It seems logical then that ocriplasmin may be less effective when there is firm or broad adhesion, as might occur with large areas of VMA. While spontaneous separation of ERMs is reported,[17,18] it is rare in adults, suggesting that ERMs have relatively firm adhesion at the macula. Given that VMT is often continuous with an ERM, the ERM may serve to anchor VMA.

We identified several other factors that appear to influence the response to ocriplasmin. Younger patients were more likely to respond, as were phakic eyes. It might instead have been expected that older patients are more responsive to ocriplasmin than younger patients, given that the vitreous becomes more synergetic with age,[19] with a weakening of VMA.[20] Likewise, it might be expected that cataract surgery weakens vitreous attachment and promotes PVD,[21-23] which occurs in up to three-fourths of patients with an attached vitreous after routine phacoemulsification surgery.[24] However, eyes that fail to develop PVD despite increasing age and cataract surgery may have firmer VMA, such that they are less likely to respond to ocriplasmin. Therefore, the worse response in older patients and pseudophakic eyes may reflect a selection bias.

Small FTMHs were more likely to close than holes with an apical diameter of >250 µm. This is consistent with the literature on FTMH closure following vitrectomy, with several authors reporting higher closure rates for small holes.[25-28]

Strengths of this study include the randomized, double-masked, placebo-controlled trial design. Responder analyses should be interpreted with caution, and the results used to generate hypotheses that can be tested in further studies, rather than to draw firm clinical conclusions.

Nonetheless, this study may help to refine case selection for eyes with symptomatic VMA/VMT, with or without FTMHs ≤400 µm. The results suggest that we should target patients with focal VMA and avoid those with an ERM. For eyes with FTMH we should target small holes (≤250 microns) rather than large ones.

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Figure Titles/Legends

Figure Titles
Figure 1. Representative OCT Images
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Figure 3. Subgroup Analysis of Vitreomacular Adhesion Resolution
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Figure 5. Subgroup Analysis of Full-Thickness Macular Hole Closure

Figure Legends
Figure 1. Optical coherence tomography (OCT) images of vitreomacular adhesion (VMA) at baseline showing: (A) broad adhesions (>1500 μm), (B) focal adhesions (≤1500 μm), and (C) full-thickness macular hole (FTMH) with VMA.

Figure 2. Forest plot showing the baseline features predictive of vitreomacular adhesion (VMA) release 28 days following treatment. The figure presents the mean odds ratios ± 95% confidence interval. Therefore, if the error bars lie to the right of 1 there is a significant difference favoring the first comparator (A, of A vs B). The figure shows younger patients were more likely to respond, as were eyes that were phakic, without an epiretinal membrane (ERM), with VMA ≤1500 microns, or with a full-thickness macular hole (FTMH).

BCVA, best-corrected visual acuity; DR, diabetic retinopathy; LCL, lower confidence limit; OR, odds ratio; TG-MV-006 and TG-MV-007, the two pivotal ocriplasmin trials; UCL, upper confidence limit. A plus sign (+) denotes that the feature was present, and a negative sign (-) that it was not.

Figure 3. The graph shows the percentages of patients with vitreomacular adhesion (VMA) resolution at day 28 in subgroups of participants with baseline features independently predictive of response. Error bars show Clopper-Pearson 95% confidence intervals.

ERM, epiretinal membrane; FTMH, full-thickness macular hole; VMA, vitreomacular adhesion.

Figure 4. The figure shows whether the baseline features were predictive of nonsurgical full-thickness macular hole (MH) closure at month 6, in a multivariate logistic regression model adjusted for baseline covariates.

LCL, lower confidence limit; MH, macular hole; OR, odds ratio; UCL, upper confidence limit.

Figure 5. The graph shows the proportion of participants with FTMH closure at month 6 in subgroups of participants with baseline features independently

predictive of response. Error bars show Clopper-Pearson 95% confidence intervals.

FTMH, full-thickness macular hole.

Figure 1. Representative OCT Images

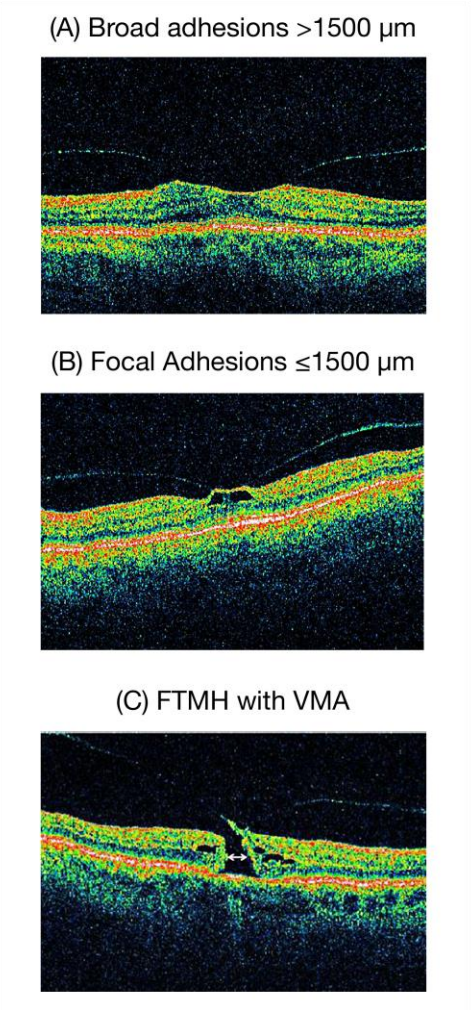

Figure 2. Baseline Features Predictive of Vitreomacular Adhesion Resolution

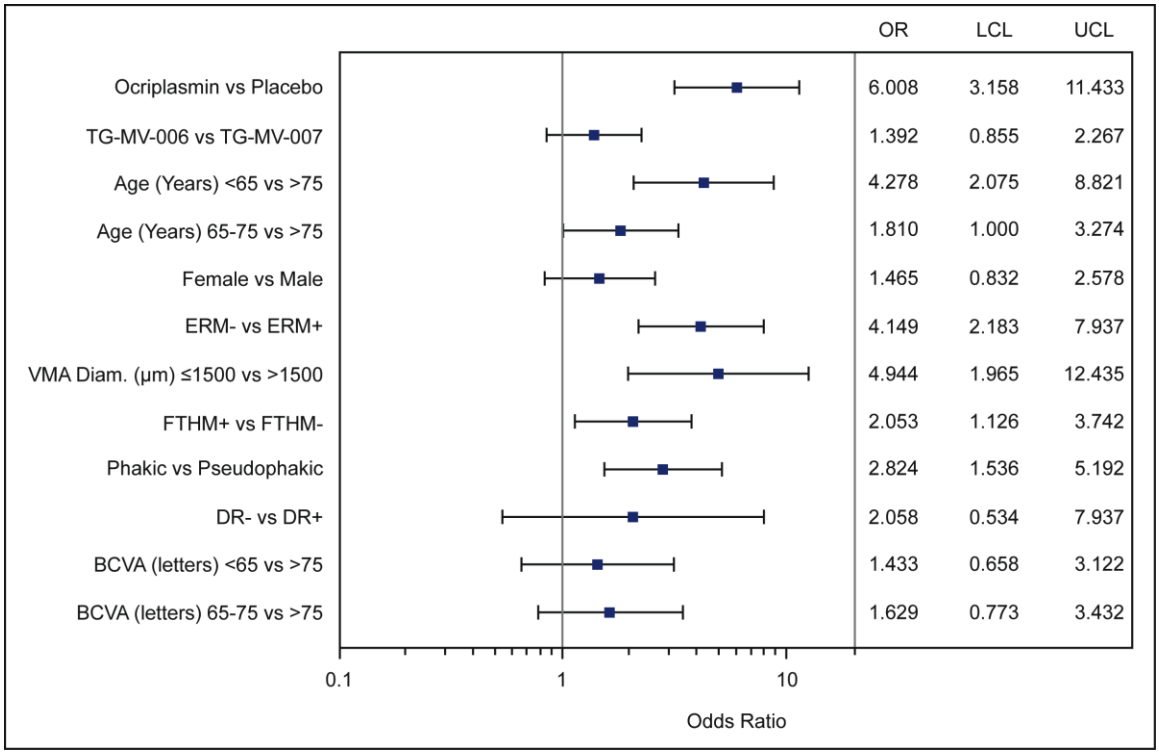

Figure 3. Subgroup Analysis of Vitreomacular Adhesion Resolution

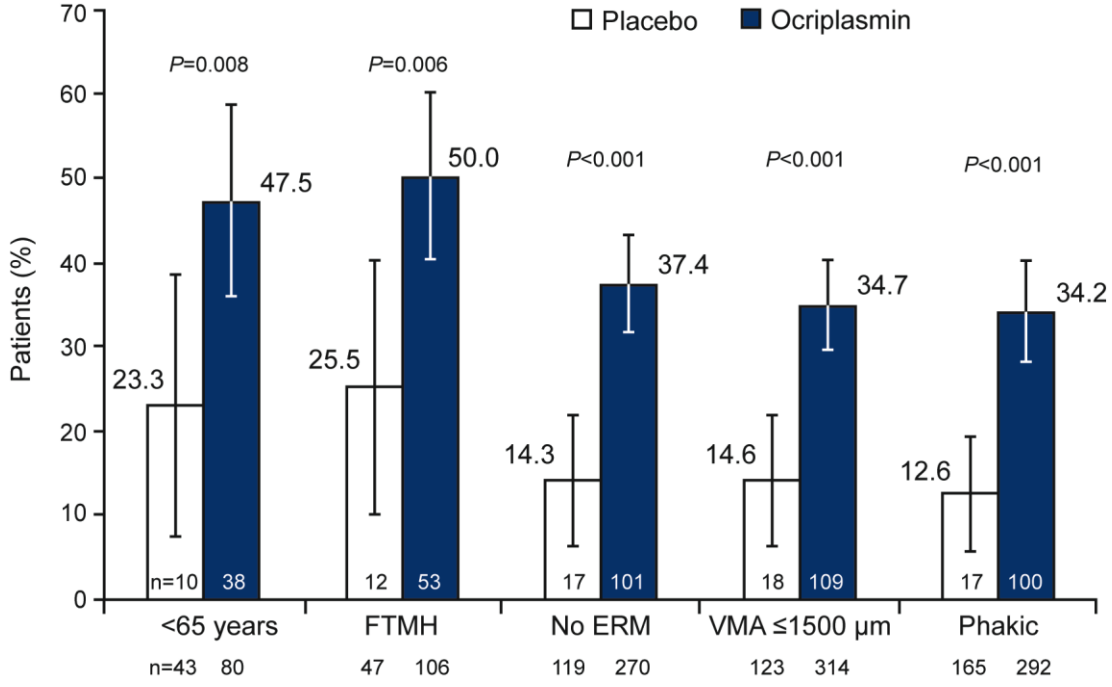

Figure 4. Baseline Features Predictive of Full-Thickness Macular Hole Closure

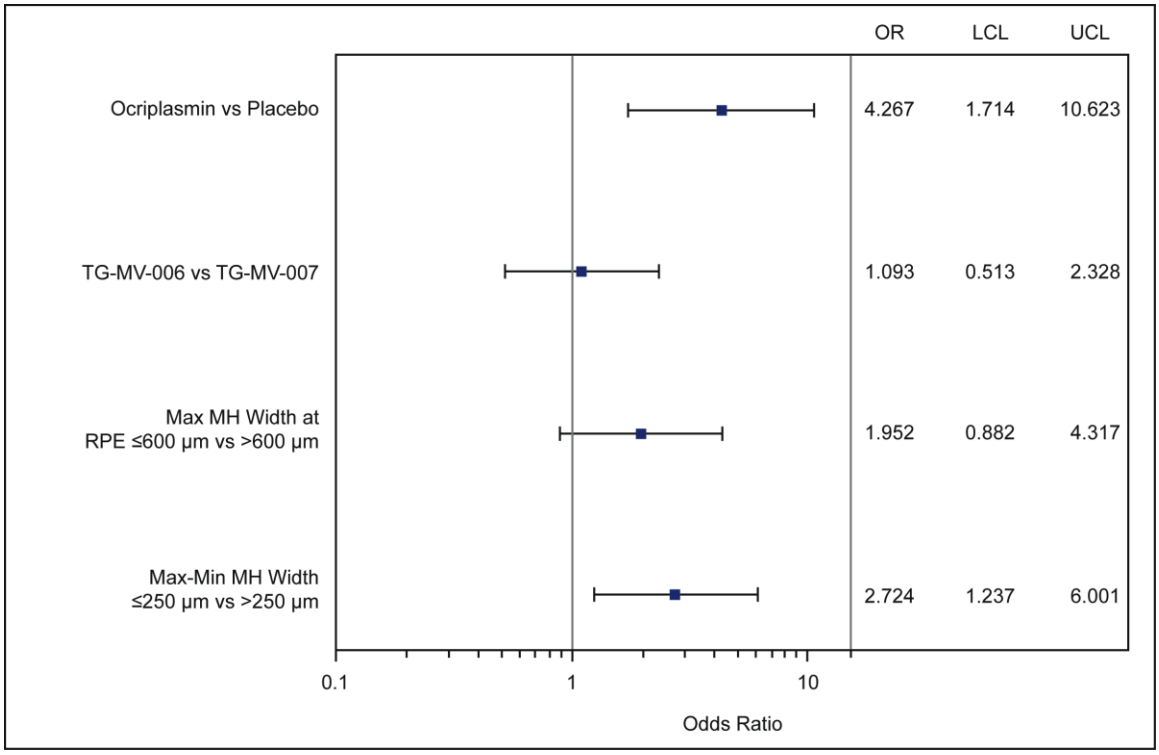

Figure 5. Subgroup Analysis of Full-Thickness Macular Hole Closure